XXXVIII.—*The Alkaloids of Ipecacuanha. Part II.*

By Frank Lee Pyman.

The first part of this investigation (Carr and Pyman, P., 1913, **29**, 226; T., 1914, **105**, 1591) characterised the then known alkaloids of ipecacuanha—emetine, cephaeline, and psychotrine—and explained their mutual relations. Psychotrine was shown to have the formula $C_{28}H_{36}O_4N_2$, and to yield on reduction a mixture of cephaeline and *iso*cephaeline, both of which had the formula $C_{28}H_{38}O_4N_2$. Emetine proved to be the monomethyl ether of cephaeline, and had the formula $C_{29}H_{40}O_4N_2$. Several crystalline derivatives of these alkaloids were described, and it was also shown that emetine gave on oxidation 6:7-dimethoxy*iso*quinoline-1-carboxylic acid, whence it followed that these three alkaloids belong to the large class of naturally occurring bases derived from *iso*quinoline.*

* After the above paper had been written, but before its publication in the Transactions, O. Hesse (*Annalen*, 1914, **405**, 1) recorded the results of an investigation on the same subject, and these were briefly discussed in an addendum to the first part of this research (*loc. cit.*, p. 1637). Hesse confirmed the formula $C_{28}H_{38}O_4N_2$ which he had previously (*Pharm. J.*, 1898,

Emetine has been largely employed for the treatment of amœbic dysentery in the Expeditionary Forces operating in hot climates, and has proved to be of great use. In some cases, however, the amœbæ responsible for the disease or its complications are not destroyed before the patient begins to show signs of emetine poisoning. It was therefore important to seek for derivatives of emetine, in which the relative toxicity to amœbæ and man should be greater than in the parent substance. An investigation of the alkaloids of ipecacuanha and their derivatives on these lines was planned in collaboration with Dr. (now temporary Lt.-Col.) C. M. Wenyon, of the Wellcome Bureau of Scientific Research, but was interrupted by his departure on active service. In view of the urgency of the matter, a number of substances were then submitted to Dr. H. H. Dale, F.R.S., of the staff of the Medical Research Committee, who, in connexion with an investigation then in progress in collaboration with Mr. C. C. Dobell, had the opportunity of testing the direct action of these substances on *Entamoeba histolytica*. Dr. Dale also made a preliminary survey of the toxic properties of these substances for the higher animals, and the two which seemed most promising have been submitted to clinical trial. The full results will be published later, but it may be recorded here that none of the compounds examined appeared to have important advantages over emetine therapeutically.*

[iv], **7**, 98) assigned to cephaeline, and also arrived at the same formula as we did for psychotrine, namely $C_{28}H_{36}O_4N_2$, but put forward for emetine the formula $C_{30}H_{40}O_5N_2$. Since, however, we have shown that emetine is the monomethyl ether of cephaeline, Hesse's formula for cephaeline, which agrees with ours, supports our formula for emetine, $C_{29}H_{40}O_4N_2$. Quite recently this formula has been confirmed by P. Karrer (*Ber.*, 1916, **49**, 2057), who also claims to have discovered independently that cephaeline yields emetine on methylation, and states that delay in consequence of the war was responsible for his failure to become acquainted with our results before he had completed his work. It may therefore be well to emphasise our priority in these discoveries by pointing out (1) that the formation of emetine by the methylation of cephaeline was the subject of British Patent No. 14677 of 1913, applied for by Wellcome, Carr, and Pyman on June 25th, 1913, published early in January, 1914, and referred to by title in the patent list of the *Chemiker Zeitung* of January 22nd, 1914, p. 107; (2) that the formula for emetine, $C_{29}H_{40}O_4N_2$, was first proposed in our preliminary note (P., 1913, **29**, 226) communicated to the Society on June 19th, 1913, whilst the full details of the whole work were described in our paper (T., 1914, **105**, 1591) published in June, 1914, and abstracted in the *Chemisches Zentralblatt* of September 23rd, 1914, p. 787. References to our work were therefore available in Germany nearly two years before the publication of Karrer's results.

* Clinical results with methylemetine sulphate have been recorded by G. C. Low, *Brit. Med.-J.*, November 13th, 1915, 715, and C. M. Wenyon and F. W. O'Connor, *J. Roy. Army Med. Corps*, 1917, **28**, 473.

The present communication (1) describes the isolation of two new alkaloids from ipecacuanha, and shows that one of them is the *O*-methyl ether of psychotrine, and (2) gives a more complete account of *N*-methylemetine and the methine derived from its methiodide.

(1) Since the isolation and separation of the three alkaloids, emetine, cephaeline, and psychotrine, from ipecacuanha by Paul and Cownley (*Pharm. J.*, 1894, [iii], **25**, 111, 373, 690), there have been indications in the literature of the presence of other alkaloids in the bark.

Merck (*Merck's Report*, 1894, p. 48) has stated that the non-phenolic ether-soluble alkaloids contain, besides emetine, another base, forming amorphous salts, whilst the phenolic ether-soluble alkaloids contain, in addition to cephaeline, a base which does not crystallise.

Hesse (*loc. cit.*) has recently described two new alkaloids, hydroipecamine and ipecamine, both of which accompany emetine, as they are non-phenolic and soluble in ether, but differ from it in failing to yield crystalline hydrobromides. The method of separation of these bases from emetine and from each other, and also the description of their properties, are not such as to inspire confidence in their homogeneity. The essential features of the separation are as follows: an aqueous solution of the mixed hydrobromides was mixed with sodium bromide, when the hydrobromides of emetine and hydroipecamine were precipitated, whilst ipecamine hydrobromide remained in solution. The precipitate was then recrystallised from water, when emetine hydrobromide crystallised out, leaving a solution of hydroipecamine hydrobromide. Hydroipecamine, $C_{25}H_{29}(OMe)_3ON_2$, was precipitated by ammonia from acid solution in white flakes, which soon become dense and "apparently crystalline." It sintered at 85°, melted at 91– 92°, and had $[\alpha]$ $-42{\cdot}2°$ ($c=2$ in 99 per cent. alcohol). No crystalline salt was obtained, but the benzoyl derivative was stated to appear distinctly crystalline under a magnification of 1100. Ipecamine, $C_{25}H_{27}(OMe)_3ON_2$, is stated to be a white, crystalline powder melting at 89—90°, and having $[\alpha]$ $-22{\cdot}5°$ ($c=2$ in 99 per cent. alcohol). Several salts and a benzoyl derivative were prepared, but none was obtained in a crystalline form. The combined yields of hydroipecamine and ipecamine from different commercial varieties of ipecacuanha were given, but the figures have little value, since they represent nothing more than the difference between the yield of non-phenolic ether-soluble alkaloids and the yield of emetine isolated in the form of the crystalline hydrobromide. Their presentation, however, is interesting in showing

that Hesse considers that the three alkaloids comprise the non-phenolic ether-soluble alkaloids of ipecacuanha. The present author is now able to show that this view is erroneous.

The non-phenolic ether-soluble alkaloids of ipecacuanha were converted into the hydrobromides and crystallised from water, when emetine hydrobromide separated. The mother liquors remaining after the separation of this salt were mixed with aqueous sodium hydroxide and extracted with chloroform. After removal of the solvent, the regenerated base was dissolved in alcohol and mived with half its weight of hydrated oxalic acid dissolved in hot alcohol, when a deposit of a crystalline hydrogen oxalate was obtained. This salt was obtained from all the commercial varieties of ipecacuanha examined, namely, Matto Grosso, Minas, Cartagena, and Johore, the yields being 0·03 to 0·06 per cent. of the weight of the bark, whilst the specific rotatory power of the crude salt varied from +34° to +38°. The crude salt is a mixture of the hydrogen oxalates of two new alkaloids, consisting principally of the hydrogen oxalate of a base which is shown below to be the O-*methyl ether of psychotrine*, but containing also the hydrogen oxalate of another base, which has been designated *emetamine*. The separation of these alkaloids presented some difficulty; fractional crystallisation of the hydrogen oxalates and hydrobromides proved unsatisfactory, but a proportion of the methylpsychotrine could be isolated by crystallisation of the sulphate. Eventually, however, it was found to be more advantageous to separate the alkaloids by fractional extraction with dilute acid from chloroform solution, when methylpsychotrine, being more basic, is removed first. It is then purified by crystallisation of the *sulphate*, which separates from water in large, well-formed, colourless prisms containing $7H_2O$; it has also been obtained as a crystalline powder containing $1H_2O$. Whilst the salt is colourless in the solid state, its concentrated aqueous solution is pale yellow; on dilution, the solution shows a beautiful blue fluorescence. The *hydrobromide*, *hydriodide*, *nitrate*, and *hydrogen oxalate* were also obtained in a crystalline form, the last when pure having $[\alpha]_D$ +41·9° for the air-dried crystals. The base has not been obtained crystalline, but a determination of its specific rotatory power in commercial absolute alcohol gave $[\alpha]_D$ +43·9°. It is much more readily soluble in dry ether than in wet ether, probably combining with water to form a hydrate, as does psychotrine.

It will be observed that methylpsychotrine, like psychotrine, is dextrorotatory, both as free base and in the form of salts. Moreover, the specific rotatory power of the sulphates of both alkaloids

remains constant at different concentrations, and the specific rotatory power of the basic ion of methylpsychotrine salts is very little different when calculated from the specific rotatory power of the sulphate, hydrobromide, and acid oxalate, the figures being $[\alpha]_D$ +65·2°, +64·2°, and +63·2° respectively. These results may be contrasted with those previously obtained with emetine and cephaeline.

Analyses of the sulphate, hydrobromide, and hydrogen oxalate were carried out, and showed that the alkaloid had the composition $C_{29}H_{38}O_4N_2$, contained four methoxyl groups, but no *N*-methyl group, and was a diacidic base. These facts at once gave rise to the suspicion that it was the *O*-methyl ether of psychotrine, and this structure was established by the partial synthesis of the compound by the methylation of psychotrine.

Methylpsychotrine is also formed by the gentle oxidation of emetine by means of alcoholic iodine, but the yield is small. When emetine is oxidised with two atomic proportions of iodine, the ensuing reaction takes the course represented by the following equation to the extent of only about 5 per cent.:

$$\underset{\text{Emetine.}}{C_{29}H_{40}O_4N_2} + I_2 = \underset{\text{Methylpsychotrine hydriodide.}}{C_{29}H_{38}O_4N_2,2HI}$$

A large proportion of the emetine is recovered unchanged, and another portion undergoes a more profound oxidation, with the production of a substance similar in properties to rubremetine, the product obtained by the oxidation of emetine with aqueous ferric chloride (Carr and Pyman, T., 1914, **105**, 1627). This result had been obtained before the author was aware of Karrer's paper in which the oxidation of emetine with a larger proportion of iodine is described. Karrer isolated a golden-yellow compound which had the formula $C_{29}H_{32}O_4N_2I$ (± one or two atoms of hydrogen), contained one non-basic and one quaternary nitrogen atom, and melted at 177—179°. He considered that this salt, which he named dehydroemetine iodide, was not identical with rubremetine hydriodide, a compound which we described as forming bright red needles having the formula $C_{29}H_{32}O_4N_2I$, containing one non-basic and one (probably) quaternary nitrogen atom, and melting from 177° (corr.) onwards. Karrer's conclusion that the two substances were different was based on a supposed greater basicity of his compound, for he found that dehydroemetine iodide could be crystallised from aqueous sodium hydroxide unchanged, whilst we had found that aqueous sodium hydroxide contained chloride after shaking with a solution of rubremetine hydrochloride in chloroform. The present author has now carried out the oxidation of emetine with eight atomic

proportions of iodine (Karrer used rather less), and isolated rubremetine from the products of the reaction in the form of its hydrochloride. This salt proves to have the properties previously described. Moreover, a specimen of rubremetine hydriodide, prepared from rubremetine hydrochloride resulting from the oxidation of emetine with ferric chloride, could be crystallised unchanged from aqueous sodium hydroxide. There is, therefore, no longer any reason to suppose that Karrer's dehydroemetine iodide is other than rubremetine hydriodide.

Methylpsychotrine, like emetine, yields rubremetine on gentle oxidation. In an attempt to prepare dibromoemetine by the addition of a molecular proportion of bromine to methylpsychotrine in cold chloroform solution, half the methylpsychotrine was recovered unchanged, whilst a portion had become oxidised to rubremetine hydrobromide. With three molecular proportions of bromine, the theoretical quantity required for the conversion of methylpsychotrine into rubremetine hydrobromide, a yield of the latter amounting to 48 per cent. of the theoretical was obtained. Emetine also yields rubremetine on treatment with bromine in cold chloroform solution.

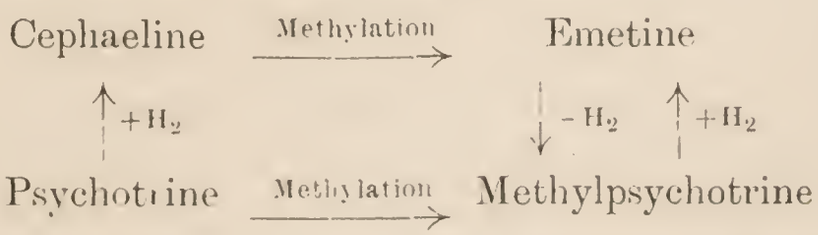
It was shown in the previous paper that psychotrine gave a mixture containing cephaeline and *iso*cephaeline when reduced with sodium and alcohol. It was therefore to be expected that methylpsychotrine would yield emetine and an isomeride, *iso*emetine, under similar conditions. This has proved to be the case, the emetine being identified as hydrobromide, and by the formation from it of *N*-methylemetine and benzoylemetine; whilst *iso*emetine, although not yet isolated in the form of a pure salt, has been shown to be present by the isolation of *benzoyliso-emetine*, a well-crystallised derivative having the formula $C_{29}H_{39}O_4N_2Bz$. The reduction of methylpsychotrine by means of sodium and alcohol leads to other substances besides emetine and *iso*emetine. On the one hand phenolic bases are formed, and on the other a new crystalline base, which may be temporarily named *base C*.* This base appears to be derived from methylpsychotrine, emetine, or *iso*emetine by the displacement of one of the methoxy-groups of the molecule by a hydrogen atom, and probably has the formula $C_{28}H_{38}O_3N_2$. It is non-phenolic, contains three methoxyl

* The letters *A* and *B* were employed in the first part of this research as temporary marks of identification for two oxidation products of cephaeline. The author prefers to designate degradation products in this way with the hope that further work may elucidate their constitution and enable them to be named correctly, rather than to coin arbitrary names for them at the present stage of the work.

groups, and is a diacidic base forming a crystalline, monacidic N-*benzoyl* derivative. Analyses of the base, its *sulphate*, *hydrogen oxalate*, and benzoyl derivative gave results which are intermediate between those required for the above formula and $C_{29}H_{38}O_3N_2$. For the present it must remain undecided whether the compound is the demethoxy-derivative of methylpsychotrine, emetine, or *iso*emetine, but it may be recorded that it could not be detected in the product obtained by the vigorous action of sodium and either ethyl or amyl alcohol on emetine.

When heated with benzoic anhydride, methylpsychotrine yields a colourless, monobasic N-*benzoyl* derivative which crystallises from ether with one molecule of ether of crystallisation, and from benzene with one molecule of benzene of crystallisation. It therefore follows that methylpsychotrine, and consequently psychotrine itself, contains an imino-group. This grouping has previously been recognised in psychotrine by Hesse (*loc. cit.*), who prepared an amorphous dibenzoyl derivative of psychotrine. The opinion expressed in our previous paper, that psychotrine was a ditertiary base, has therefore proved to be incorrect. The formation of cephaeline and *iso*cephaeline by the reduction of psychotrine, and of emetine and *iso*emetine by the reduction of methylpsychotrine, is consequently due to the reduction of a C:C, and not of a C:N linking. The occurrence of two isomeric forms of the reduced base in each case indicates that at least one of the carbon atoms of the group C:C is rendered asymmetric by the addition of hydrogen.

The relations of methylpsychotrine to the previously known alkaloids of ipecacuanha are now clear, and the interconversions of the four alkaloids, which have been realised experimentally, may be recorded diagrammatically as follows:



Emetamine was isolated in a partly purified condition from the least basic fraction of its mixture with methylpsychotrine. It was purified by crystallisation of the *hydrobromide*, liberation from this, and crystallisation as base, when it formed colourless needles which melted at 155—156° (corr.). Analyses of the base, hydrobromide, and *hydrogen oxalate* gave figures intermediate between those required for the formulæ $C_{29}H_{36}O_4N_2$ and $C_{30}H_{36}O_4N_2$. Emetamine contains four methoxyl groups, but no *N*-methyl group, is non-phenolic, and a diacidic base. It does not yield a benzoyl

derivative when heated with benzoic anhydride, but remains unchanged. On reduction with sodium and alcohol, it gives a product which, after benzoylation, yields a small quantity of benzoyl-*iso*emetine. It is therefore probable that emetamine has the formula $C_{29}H_{36}O_4N_2$, and differs from emetine in containing two unsaturated linkings, one of them connecting two carbon atoms and the other a carbon and a nitrogen atom. It does not, however, appear to be an intermediate product between methylpsychotrine and rubremetine, for it is not contained amongst the products of the oxidation of emetine with iodine, or of methylpsychotrine with bromine, where its presence would be indicated by a low specific rotatory power of the methylpsychotrine hydrogen oxalate formed or recovered.

The base is dextrorotatory, having $[\alpha]_D$ +12·3° in absolute alcohol, whilst the salts are lævorotatory. The specific rotatory powers of the basic ion of emetamine salts in aqueous solution are widely different when calculated from those of the hydrobromide and hydrogen oxalate; thus, for a concentration of 2·6 per cent. of alkaloid in each case, the specific rotatory power of the basic ion calculated from that of the hydrobromide is $[\alpha]_D$ −35·3°, and from that of the hydrogen oxalate $[\alpha]_D$ −8·9°. Emetine salts have previously been shown (T., 1914, **105**, 1598) to give similar results.

The original material, the crude hydrogen oxalate, does not appear to contain other alkaloids besides methylpsychotrine and emetamine, and consequently, since the specific rotatory power of the hydrogen oxalates of the pure alkaloids, as well as that of the mixture, is known, it is possible to calculate the proportion of each present. It is thus found that the different commercial varieties of ipecacuanha contain from 0·015 to 0·033 per cent. of methylpsychotrine and 0·002 to 0·006 per cent. of emetamine, expressed as alkaloid in each case. Since the hydrobromides of both alkaloids are precipitated by sodium bromide, they are probably constituents of Hesse's hydroipecamine hydrobromide. They cannot, however, form a large proportion of this substance, since the free bases are dextrorotatory, whilst hydroipecamine is lævorotatory under the same conditions.

(2) A further study of *N*-methylemetine and its salts has been made. Fractional crystallisation of a large quantity of the hydrobromide brought about no separation, the first and last fractions both having the properties previously described for this salt. The base has not been obtained in a crystalline form, but an approximate determination of its specific rotatory power in chloroform gave the figure $[\alpha]_D$ −53°. The *sulphate* has now been

crystallised, and the analyses of this salt confirm the formula, $C_{30}H_{42}O_4N_2$, previously put forward for *N*-methylemetine.

Some preliminary experiments on the degradation of emetine by Hoffmann's method have been made. Hesse (*loc. cit.*) first prepared the methine from emetine by treating methylemetine methiodide with silver hydroxide and evaporating the solution. The crude methine was then dissolved in aqueous acetic acid and precipitated by ammonia, when it was obtained as a white powder melting at 52°, which is described as apparently crystalline. On analysis, it gave figures (C = 71·48; H = 8·24) in agreement with those required for the formula $C_{32}H_{44}O_5N_2$, which Hesse attributed to it.

This formula for the methine differs considerably in carbon content from that required by our formula for emetine, and it was therefore necessary to repeat the preparation of the methine. This was accordingly done (in March, 1915), but, in the meantime, Karrer (*loc. cit.*) has also prepared and described the methine. He evaporated a solution of the methohydroxide first under normal pressure and then in a vacuum, and distilled the residue under 3 mm. pressure, when it formed a glassy mass. The distillate was dissolved in ether and treated with gaseous hydrogen chloride, when the methine hydrochloride was precipitated. Analyses of this salt led to the formula $C_{32}H_{46}O_4N_2,2HCl$, which corresponds with the formula $C_{29}H_{40}O_4N_2$ for emetine. It will be observed that neither Hesse nor Karrer established the purity of their preparations of the methine by recrystallisation of the base or a salt, and were therefore unable to prove the homogeneity of their compounds. It might appear that their failure to crystallise the methine was due to this substance being a mixture of stereoisomerides. Karrer has shown that one of the nitrogen atoms of the emetine molecule is a tertiary nitrogen atom common to two ring complexes like the nitrogen atom in canadine, and the author has shown previously (T., 1913, **103**, 817) that the degradation of canadine by heating the methohydroxide in a vacuum on the water-bath yields a mixture of three isomeric methines. It was therefore possible that methylemetine methohydroxide would behave similarly, and that consequently the methines of Hesse and Karrer were mixtures of isomerides. The present investigation, however, has shown that the total methine consists mainly, if not entirely, of an individual substance. The methine was prepared by evaporating a solution of the methohydroxide in a vacuum. A large number of its salts were prepared, and eventually one, the neutral *oxalate*, became crystalline. This salt crystallises very well from water, in which it is readily soluble, and was purified

by this means, a yield of 77 per cent. of the theoretical being obtained. On analysis, it proved to have the composition $C_{32}H_{46}O_4N_2,C_2H_2O_4,7\frac{1}{2}H_2O$. When dissolved in water and precipitated by ammonia, it yields the base as a white powder which melts at 45—55°. Hesse's view that the methine is apparently crystalline cannot be confirmed, for no structure was apparent under the microscope, and the white powder gradually set to a glass-like mass on keeping. Analyses of the base prepared from the pure oxalate gave figures in agreement with those required for the formula $C_{32}H_{46}O_4N_2$, and thus serve to confirm the formula $C_{29}H_{40}O_4N_2$ for emetine, from which the methine is derived as follows:

$$\underset{\text{Emetine.}}{C_{29}H_{40}O_4N_2} \longrightarrow \underset{N\text{-methylemetine.}}{C_{30}H_{42}O_4N_2} \longrightarrow \underset{\substack{N\text{-methylemetine}\\ \text{methohydroxide.}}}{C_{32}H_{48}O_4N_2(OH)_2} \longrightarrow$$

$$\underset{N\text{-methylemetinemethine.}}{C_{32}H_{46}O_4N_2}$$

Experimental.

Isolation of Methylpsychotrine and Emetamine from Ipecacuanha.

In the preparation of emetine, the alkaloids of ipecacuanha are dissolved in ether and the solution is extracted with dilute aqueous sodium hydroxide to remove cephaeline and other phenolic substances. The non-phenolic alkaloids remaining in the ethereal solution are then converted into hydrobromides and crystallised from water, when emetine hydrobromide separates. The mother liquors gradually deposit further crops of this salt after being concentrated and kept. When the separation of the crystals is complete, the bases are regenerated into ether or chloroform, and the solvent is removed. The remaining syrup (1 part) is dissolved in alcohol (2 parts) and mixed with a hot solution of hydrated oxalic acid (0·5 part) in alcohol (5 parts), when a hydrogen oxalate separates in small rosettes of fine needles. All the commercial varieties of ipecacuanha root give a crystalline oxalate in this way, and the yields obtained from the different varieties are recorded below, together with the specific rotatory power of the air-dried material in aqueous solution. The crude salt has no sharp melting point, but sinters and melts without flowing from 145° to 150° after drying in a vacuum over sulphuric acid. It is a mixture of the hydrogen oxalates of methylpsychotrine and emetamine, which, when pure, have the specific rotatory powers $[\alpha]_D$ +41·9° and −6° respectively in the air-dried state. Since no other alkaloid appears to be present, the yields of the two bases

from the different varieties of ipecacuanha can be calculated, and these results are also given in the following table:

	Yield of air-dried hydrogen oxalate. Per cent	$[\alpha]_D$	Methyl-psychotrine. Per cent.	Emetamine. Per cent.
Matto Grosso (1) ...	0·039	+35°	0·022	0·004
,, ,, (2) ...	0·059	+34·1°	0·033	0·006
Minas	0·026	+36·5°	0·015	0·002
Cartagena.....	0·038	+35°	0·021	0·004
Johore	0·048	+35·6°	0·028	0·004

On another occasion the crude hydrogen oxalate from Matto Grosso root had $[\alpha]_D$ +37·7°.

Various methods were tried for the separation of the alkaloids from each other. Fractional crystallisation of the hydrogen oxalates from water effected very little separation as a rule, but occasionally first crops with $[\alpha]_D$ about +33° were obtained.

Fractional crystallisation of the hydrobromides from aqueous solution slowly effected the separation of a hydrobromide of lower specific rotatory power. Thus, in a series of fractional crystallisations of the crude salt from two to four parts of water, the specific rotatory power of the first crop fell as follows: from +35°, to +31°, +27·5°, +21°, and +17·1°, a quantity of more than 300 grams of the mixed hydrobromides giving 10 grams of salt having $[\alpha]_D$ +17·1°. Further purification of this salt was suspended. There were then obtained, after about fifty crystallisations, 62 grams in various crops having $[\alpha]_D$ from +27° to +38° and 190 grams having $[\alpha]_D$ about +45°, calculated in this case for the anhydrous salt Finally, the mother liquors were converted into the hydrogen oxalate, giving 43 grams having $[\alpha]_D$ +41° for the air-dried salt. Comparison of these figures with the specific rotatory powers of the pure salts of methylpsychotrine shows that this base was concentrated in the later fractions, the last consisting of nearly pure methylpsychotrine hydrogen oxalate.

Fractional crystallisation of the sulphates from water gave a better result, the sulphate of methylpsychotrine separating in large, colourless prisms, which were readily purified by crystallisation from water, but only a fraction of the methylpsychotrine could be isolated in this way.

Eventually a suitable method of separation was found in fractional extraction of the bases from their solution in chloroform by means of dilute sulphuric acid, when methylpsychotrine, the more basic of the two, is removed first. This was carried out in the following manner.

Six hundred grams of the crude hydrogen oxalate having $[\alpha]_D$ +37·7° were basified with sodium hydroxide and extracted

with chloroform. The chloroform solution was extracted with 61·5 grams of sulphuric acid (three-quarters of the calculated amount) in 1200 c.c. of water and separated from the chloroform solution (*A*), the acid solution being washed with chloroform and the chloroform solution with water. The base was liberated from the acid extract by sodium hydroxide and extracted with chloroform, and again about three-quarters of the amount was extracted by means of dilute sulphuric acid, leaving a chloroform solution (*B*). The aqueous solution of the sulphate was evaporated to dryness on the water-bath under diminished pressure, boiled with a little alcohol, and again evaporated to dryness, the last two operations being repeated until the residue appeared wholly crystalline. It was then boiled with a large volume of alcohol, and the insoluble, nearly colourless, crystalline powder was collected. This was the monohydrate of methylpsychotrine sulphate, and amounted to 306 grams having $[\alpha]_D$ +50·8°. Further fractionation in the same manner gave a first crop, having the specific rotatory power of the pure salt, $[\alpha]_D$ +53°, which was then purified from a little colouring matter by crystallisation from its own weight of hot water, when the pure heptahydrate separated in large, colourless crystals. The chloroform solution (*B*) was distilled to remove the solvent and the residue was converted into the hydrogen oxalate, when 92 grams of the mixed hydrogen oxalates having $[\alpha]_D$ +37·6° were obtained.

The chloroform solution (*A*) was extracted three times with 5 per cent. aqueous sulphuric acid, using 100 to 110 c.c. each time, and the extracts were evaporated to give the monohydrate in the manner described above. They gave respectively 27·8 grams, $[\alpha]_D$ +51·2°; 32·6 grams, $[\alpha]_D$ +49·4°; and 28·1 grams, $[\alpha]_D$ +32·6°. The remaining chloroform was then distilled, and the residue converted into the hydrogen oxalate, when 17·6 grams having $[\alpha]_D$ −1·4° were obtained. Further fractionation of this material gave a small amount of dextrorotatory hydrogen oxalate, and finally a number of fractions having $[\alpha]_D$ −5°. This partly purified emetamine hydrogen oxalate was dissolved in water, basified by aqueous sodium hydroxide, and extracted with ether. After drying the ethereal extract with anhydrous potassium carbonate and distilling the solvent, the residue was converted into the hydrobromide and crystallised fractionally from water. Finally, the base was regenerated from the hydrobromide by shaking with chloroform and aqueous sodium hydroxide. After distilling the chloroform, the base remained as an oil which soon became crystalline, and was purified by recrystallisation from ethyl acetate.

The Properties of O-Methylpsychotrine and its Salts.

The *base* has not been obtained in a crystalline form. It is readily soluble in chloroform, or in dry ether, but sparingly so in moist ether. When an aqueous solution of a methylpsychotrine salt is made alkaline, somewhat large quantities of ether are necessary to extract the base, but the ethereal solution when dried can be concentrated to a small volume without any separation taking place. This behaviour suggests that methylpsychotrine combines with water to form a hydrate, as does psychotrine. An ethereal solution of the base is colourless at first, but gradually becomes brown on keeping or when concentrated on the water-bath. Solutions of the base in organic solvents are not fluorescent, but dilute aqueous solutions of the salts are fluorescent. Methylpsychotrine is precipitated as a viscous oil on the addition of alkalis to aqueous solutions of its salts; it is soluble in excess of ammonia, but not in excess of sodium carbonate or hydroxide. It dissolves in concentrated sulphuric acid, giving a very pale yellow solution tinged with green; on the addition of a drop of nitric acid to this solution the colour becomes orange-brown. The base dissolves in Froehde's reagent, giving an emerald-green solution.

An approximate determination of the specific rotatory power of the base was made in commercial absolute alcoholic solution in the following manner. A quantity of the pure sulphate was regenerated to ether by sodium carbonate. The ethereal solution was dried with anhydrous potassium carbonate and distilled on the water-bath first under normal and finally under diminished pressure to remove the ether. The nearly colourless residue was dissolved in commercial absolute alcohol and made up to 50 c.c. Five c.c. of this required 8·10 c.c. of $N/10$-sulphuric acid, using cochineal, whence $c = 3{\cdot}876$:

$$\alpha_D + 3{\cdot}40°;\ c = 3{\cdot}876;\ l = 2\text{-dcm.};\ [\alpha]_D + 43{\cdot}9°.$$

After diluting 14·5 c.c. of this solution to 27·0 c.c., the following result was obtained:

$$\alpha_D + 1{\cdot}92°;\ c = 2{\cdot}081;\ l = 2\text{-dcm.};\ [\alpha]_D + 46{\cdot}1°.$$

Methylpsychotrine sulphate crystallises from water in large, hard, colourless prisms containing $7H_2O$. It is soluble in little more than its own weight of water, giving a pale yellow solution, which is neutral to litmus and has a bitter taste. Dilute solutions show a beautiful blue fluorescence. The crystals of the heptahydrate have triboluminescent properties, giving a blue flash when ground in the dark. On heating, the air-dried salt softens and loses water at 80—100°, turns yellow at about 220°, and melts and effervesces at 247° (corr.). After dehydration under diminished pressure over sulphuric acid, however, it remains as an amorphous powder,

which becomes pink-coloured in the light, and softens and becomes transparent at 160—170° (corr.).

Found, in the air-dried salt: $H_2O = 18{\cdot}1$, 17·9, 18·0; $SO_4 = 13{\cdot}9$.
$C_{29}H_{38}O_4N_2,H_2SO_4,7H_2O$(702·7) requires $H_2O = 17{\cdot}9$;
$SO_4 = 13{\cdot}7$ per cent.

The specific rotatory power of the air-dried heptahydrate was determined in aqueous solution:

α_D +7·15°; $c = 8{\cdot}062$; l = 2-dcm.; $[\alpha]_D$ +44·4°.
α_D +3·67°; $c = 4{\cdot}132$; l = 2-dcm.; $[\alpha]_D$ +44·4°, whence for the anhydrous sulphate $[\alpha]_D$ is +54·1°.

Methylpsychotrine sulphate can also be obtained as a monohydrate in the following way. A concentrated filtered solution of the heptahydrate is quickly evaporated to dryness on the water-bath under diminished pressure, and the amorphous residue is boiled with commercial absolute alcohol, when the salt dissolves and quickly separates as a colourless, crystalline powder. After drying under diminished pressure over suphuric acid, this salt begins to turn yellow at about 220° and melts and effervesces at 247° (corr.).

Found, in the air-dried salt: $H_2O = 3{\cdot}1$, 3·4; C = 58·2; H = 7·1.
$C_{29}H_{38}O_4N_2,H_2SO_4,H_2O$(594·6) requires $H_2O = 3{\cdot}0$; C = 58·6;
H = 7·1 per cent.

Found, in the dried salt: C = 60·2; H = 7·2.
$C_{29}H_{38}O_4N_2,H_2SO_4$ (576·5) requires C = 60·4; H = 7·0 per cent.

The specific rotatory power of the air-dried monohydrate was determined in aqueous solution:

α_D +4·42°; $c = 4{\cdot}195$; l = 2-dcm.; $[\alpha]_D$ +52·7°, whence for the anhydrous sulphate $[\alpha]_D$ is +54·3°.

Methylpsychotrine hydrobromide crystallises from water in pale yellow, silky needles. After drying in the air it contains a variable amount of water of crystallisation.

Found, in the air-dried salt: $H_2O = 10{\cdot}5$, 16·9, 18·7.
$C_{29}H_{38}O_4N_2,2HBr + 4H_2O$ requires $H_2O = 10{\cdot}1$; $+8H_2O$ requires
$H_2O = 18{\cdot}4$ per cent.

After drying in a vacuum over sulphuric acid this salt has no sharp melting point, but softens and becomes transparent from about 190° to 200° (corr.).

Found, in the dried salt: C = 54·1, 54·1, 54·7; H = 6·8, 6·9, 6·5;
Br = 24·95, 24·83; OMe = 19·5, 19·0; NMe = 0.
$C_{29}H_{38}O_4N_2,2HBr$ (640·3) requires C = 54·4; H = 6·3; Br = 24·96;
4OMe = 19·4 per cent.

The specific rotatory power of the anhydrous salt was determined in aqueous solution:

α_D +1·58°; c = 1·645; l = 2-dcm.; $[\alpha]_D$ +48·0°.

This salt is very readily soluble in water. It is precipitated from its concentrated aqueous solutions by a saturated solution of sodium bromide, separating as an oil which crystallises on keeping.

Methylpsychotrine hydrogen oxalate separates from alcohol in small rosettes of fine, white needles, which contain $3\frac{1}{2}H_2O$. After drying in a vacuum over sulphuric acid, it begins to soften at about 150°, gradually melts up to 155°, and effervesces at 162° (corr.). It is readily soluble in water, but very sparingly so in alcohol.

Found, in the air-dried salt: loss at 110°, H_2O = 8·5.

$C_{29}H_{38}O_4N_2,2C_2H_2O_4,3\frac{1}{2}H_2O$ (721·6) requires H_2O = 8·7 per cent.

Found, in the salt dried at 110°: C = 60·0, 60·0; H = 6·6, 6·5.

$C_{29}H_{38}O_4N_2,2C_2H_2O_4$ (658·5) requires C = 60·2; H = 6·4 per cent.

The specific rotatory power of the air-dried salt was determined in aqueous solution:

α_D +3·57°; c = 4·265; l = 2-dcm.; $[\alpha]_D$ +41·9°, whence for the anhydrous salt $[\alpha]_D$ is +45·9°.

Methylpsychotrine hydriodide and *nitrate* also crystallise well.

The Methylation of Psychotrine. Formation of Methylpsychotrine.

A small quantity of psychotrine was methylated by the method previously described (T., 1914, **105**, 1624), and the non-phenolic alkaloid, which was extracted by ether, was converted into the hydrogen oxalate The small quantity available (0·5 gram) did not allow of complete purification, but sufficed to establish the identity of the substance. It formed small rosettes of fine needles, readily soluble in water, but very sparingly so in alcohol.

After drying in a vacuum, it began to soften at 150° and formed a viscous, translucent mass on further heating.

The specific rotatory power of the air-dried hydrogen oxalate was determined in aqueous solution:

α_D +2·02°; c = 2·451; l = 2-dcm.; $[\alpha]_D$ +41·2°.

The base was then regenerated and converted into the sulphate (monohydrate), which, after drying, melted at 241°, the pure natural salt melting at 246° and the mixture at 242° (corr.) in the same bath.

The specific rotatory power of the dried sulphate was determined in aqueous solution:

α_D +1·25°; c = 1·179; l = 2-dcm.; $[\alpha]_D$ +53·0° for the anhydrous salt.

Finally, the salt recovered from this determination was allowed

to crystallise from water, when it formed the characteristic prismatic crystals of methylpsychotrine sulphate heptahydrate. These had the correct melting point, sintering at about 80°, turning yellow at about 220°, and melting and effervescing at 247° (corr.).

The Oxidation of Emetine with Alcoholic Iodine. Formation of Methylpsychotrine and Rubremetine.

(1) *Using One Molecular Proportion of Iodine.*—A preliminary experiment having shown that the yield of methylpsychotrine was very small, it was necessary to establish the fact that none was contained in the starting material. Accordingly, 10 grams of emetine hydrobromide were recrystallised from 50 c.c. of water, when 9·0 grams of air-dried salt were obtained. The mother liquors, basified and extracted with ether, gave 0·5 gram of base, which was dissolved in 1 c.c. of alcohol, mixed with a solution of 0·25 gram of hydrated oxalic acid in 2·5 c.c. of alcohol, and kept. No crystals separated even after inoculating with a crystal of methylpsychotrine hydrogen oxalate.

The 9·0 grams of emetine hydrobromide were then dissolved in water, basified with sodium hydroxide, and extracted with ether. The ethereal residue was dissolved in 80 c.c. of absolute alcohol, mixed with 3·2 grams of powdered iodine, and heated in an autoclave for four hours at 100°. The product was mixed with 200 c.c. of dilute sulphurous acid, and evaporated to about half its volume on the water-bath under diminished pressure. The solution, containing solid matter in suspension, was completely extracted with chloroform, and this was shaken well with dilute sodium hydroxide to liberate the free bases from the iodides of tertiary bases contained in it. The chloroform solution was then completely extracted with dilute hydrochloric acid, dried, and distilled, when it left 1·7 grams of dark brown resin.

The acid extract was made alkaline with sodium hydroxide and extracted with ether. After distillation of the ether, 5·4 grams of alkaloid remained. This was converted into and crystallised as the hydrobromide, which was recrystallised once from a little water, when 4·0 grams of air-dried emetine hydrobromide were recovered. The mother liquors of the two crystallisations were basified with sodium hydroxide, and extracted with ether, when 1·5 grams of alkaloid were obtained. This material was dissolved in 3 c.c. of alcohol, mixed with a solution of 0·8 gram of hydrated oxalic acid in 8 c.c. of alcohol, seeded with methylpsychotrine hydrogen oxalate, and kept, when rosettes of small needles separated. These were collected, and amounted to 0·23 gram after thorough washing with alcohol and drying in the air.

The identity of this substance with methylpsychotrine hydrogen oxalate was shown as follows. After drying at 100°, the substance sintered from 145° and gradually melted up to 150° (corr.), whilst a specimen of methylpsychotrine hydrogen oxalate sintered from 150° and melted at 155° in the same bath, a mixture of the two compounds melting at an intermediate temperature. The air-dried hydrogen oxalate had the correct specific rotatory power in aqueous solution within the limits of experimental error:

$$\alpha_D + 0{\cdot}85°;\ c = 1{\cdot}051;\ l = 2\text{-dcm.};\ [\alpha]_D + 40{\cdot}4°.$$

The base regenerated from a solution of the hydrogen oxalate was converted into the sulphate (monohydrate), when it was obtained as a colourless, crystalline powder, readily soluble in water, but sparingly so in absolute alcohol. After drying at 100°, it melted and decomposed at 247° (corr.), turning yellow earlier, whilst methylpsychotrine sulphate melted at 248° in the same bath and a mixture of the two substances at 247°.

(2) *Using Four Molecular Proportions of Iodine.*—3·57 Grams of emetine hydrobromide were dissolved in water, basified with sodium hydroxide, and extracted with ether. After removing the solvent, the base was dissolved in 50 c.c. of absolute alcohol, mixed with 5·08 grams of iodine, and heated in an autoclave for four hours at 100°. The product was mixed with sodium carbonate solution, filtered, suspended in water, and treated with sulphurous acid. The golden-brown precipitate was then collected, and extracted repeatedly with boiling water, until nearly all had dissolved. The aqueous solution, amounting to 1·5 litres, was boiled with excess of silver chloride, filtered through kieselguhr, and evaporated under diminished pressure to a volume of about 50 c.c. A few c.c. of concentrated hydrochloric acid were then added, when 0·55 gram of rubremetine hydrochloride separated in minute, orange-red needles. This salt was purified by dissolving it in chloroform, evaporating the solution to dryness, dissolving the residue in acetone, and adding water—the method previously described (T., 1914, **105**, 1628) for the purification of rubremetine hydrochloride—when it separated in orange-red needles, which appeared scarlet when dry. The air-dried salt melted at 124° (corr.), whilst a specimen of rubremetine hydrochloride, prepared by the oxidation of emetine with ferric chloride, melted at 127° (corr.) in the same bath, and a mixture of the two substances melted between these temperatures. After drying at 100°, no difference between the melting points of the specimens from the two sources was observed, both melting and effervescing at about 173° (corr.) after sintering earlier.

The aqueous filtrate from this salt was basified with sodium hydroxide and extracted with ether, when 0·6 gram of a mixture

of emetine with a little methylpsychotrine was removed. The liquor was then acidified with hydrochloric acid and extracted completely with chloroform, which left 0·4 gram of residue on distillation. This material gave a little more rubremetine hydrochloride on crystallisation from water.

The Action of Bromine on Methylpsychotrine. Formation of Rubremetine.

(1) *Using One Molecular Proportion of Bromine.*—Seven grams of methylpsychotrine sulphate heptahydrate were dissolved in water, basified with sodium carbonate, and extracted with chloroform, the extract (about 100 c.c.) being dried with anhydrous potassium carbonate and filtered. To it a solution of 0·5 c.c. of bromine in 40 c.c. of chloroform was added at the ordinary temperature, and after five minutes the yellow solution was shaken with dilute ammonium hydroxide, dried with potassium carbonate, and distilled. The residue was extracted twice with 50 c.c. of boiling water, and the aqueous extracts were combined, filtered, and concentrated, when 1·45 grams of air-dried rubremetine hydrobromide were deposited in minute, red needles melting at 115—120° (corr.). (Found, in dried salt: Br = 14·2. Calc., Br = 14·4 per cent.)

The material, which was insoluble in water, was dissolved in dilute hydrochloric acid, made alkaline with ammonia, and extracted with ether. The ether residue was dissolved in alcohol and mixed with alcoholic oxalic acid, when 3·3 grams of methylpsychotrine hydrogen oxalate were recovered unchanged, having the correct melting point and $[\alpha]_D$ +41·5° for the air-dried salt in aqueous solution.

(2) *Using Three Molecular Proportions of Bromine.*—A chloroform solution of the base from 7 grams of methylpsychotrine sulphate heptahydrate was treated with a solution of 1·5 c.c. of bromine in chloroform and worked up as in the previous experiment, when 3·3 grams of air-dried rubremetine hydrobromide were obtained, a yield of 48 per cent. of the theoretical.

N-*Benzoyl*-O-*methylpsychotrine.*

Nine grams of methylpsychotrine sulphate (containing $7H_2O$) were dissolved in water, and the base was regenerated to ether by means of sodium hydroxide. The ethereal solution was dried with anhydrous potassium carbonate, filtered, and mixed with 12 grams of benzoic anhydride. The ether was then removed by distillation and the residue heated for three-quarters of an hour in the water-bath. It was then dissolved in ether and extracted with very dilute hydrochloric acid. The latter was washed with more ether,

then made alkaline with ammonia, and extracted with ether. The ethereal solution was dried with anhydrous potassium carbonate and distilled to a volume of about 30 c.c., when 5·2 grams of benzoylmethylpsychotrine separated, whilst the mother liquor gave a second crop of 1·0 gram. Both crops melted and effervesced at 78—80° (corr.). The substance was purified by dissolving it in warm ether, filtering from a small quantity of amorphous matter, and concentrating the solution, when it formed hexagonal plates melting as before.

The air dried substance contains a molecular proportion of ether of crystallisation which is expelled at 60—85°/15 mm.; the base then remains in an amorphous form, and has no sharp melting point, but begins to sinter at about 100° and then gradually melts. The air-dried base containing ether of crystallisation only loses 1—2 per cent. by weight when dried in a vacuum over sulphuric acid at the ordinary temperature.

Found, in air-dried base: loss at 60—85°/15 mm., 11·5; C = 73·0, 73·0; H = 8·0, 8·0.

$C_{36}H_{42}O_5N_2,Et_2O$ (656·6) requires Et_2O = 11·3; C = 73·1; H = 8·0 per cent.

Found in base dried at 60—85°/15 mm.: C = 74·2; H = 7·5.

$C_{36}H_{42}O_5N_2$ (582·5) requires C = 74·2; H = 7·3 per cent.

The presence of a molecular proportion of ether in the air-dried base was confirmed by a determination of the alkyloxyl groups present by the modification of Zeisel's method employed for very volatile compounds (*Monatsh.*, 1886, **7**, 406): 0·2604 air-dried base gave 0·5364 AgI, whilst the amount calculated for a substance, $C_{40}H_{52}O_6N_2$, containing six alkyloxyl groups is 0·5586 AgI.

The specific rotatory power of the air-dried base was determined in chloroform solution:

$$\alpha_D + 1·75°;\ c = 2·389;\ l = 2\text{-dcm.};\ [\alpha]_D + 36·6°.$$

Benzoylmethylpsychotrine, containing ether of crystallisation, is insoluble in water or dilute alkalis, but dissolves in very dilute acids. It is easily soluble in alcohol, acetone, ethyl acetate, benzene, or chloroform, sparingly so in cold ether, more readily so in hot ether, and very sparingly so in light petroleum.

On crystallising this substance from benzene, the molecule of ether of crystallisation is replaced by a molecule of benzène. The substance is then obtained in colourless, hexagonal plates, which, when placed in a bath at 115°, begin to sinter at 120° and melt and effervesce at 135° (corr.). The air-dried crystals from benzene suffer no loss in a vacuum over sulphuric acid; when heated to 100°, they lose about 4 per cent. by weight, but become discoloured.

Found, in the air-dried base: C = 76·6, 76·9, 76·8; H = 7·3, 7·5, 7·4; OMe = 19·2.

$C_{36}H_{42}O_5N_2,C_6H_6$ (660·6) requires C = 76·3; H = 7·3; 4OMe = 18·8 per cent.

The base was titrated with sulphuric acid in aqueous alcoholic solution, using cochineal as indicator. The end-point was not sharp, but the result indicates clearly that the substance is monobasic:

0·3857 air-dried base (from benzene) required 5·9 c.c. $N/10$-H_2SO_4; whence equivalent = 654.

The specific rotatory power of this substance was determined in chloroform solution:

$$\alpha_D + 1·33°;\ c = 1·818;\ l = 2\text{-dcm.};\ [\alpha]_D + 36·6°.$$

*Reduction of Methylpsychotrine with Sodium and Alcohol. Isolation of Emetine, Benzoyl*isoemetine, *and Base* C.

Fifteen grams of methylpsychotrine sulphate (containing $7H_2O$) were dissolved in water and the base was regenerated into ether. The ethereal residue was dissolved in 20 c.c. of absolute alcohol, 15 grams of sodium were added, and the mixture was heated under a reflux condenser on the water-bath, whilst 200 c.c. of absolute alcohol were added slowly during one hour. A little water was then added to decompose a few undissolved fragments of sodium, followed by sufficient concentrated hydrochloric acid (about 75 c.c.) to acidify the liquor. The sodium chloride which separated was collected, washed with alcohol, and rejected. The filtrate was evaporated to a small bulk under diminished pressure, and the residue dissolved in water. From this solution the bases were regenerated into ether, and separated into non-phenolic bases (7—8 grams) and phenolic bases (2—3 grams) in the usual way.

The non-phenolic bases were dissolved in a hot solution of 4 grams of hydrated oxalic acid in 100 c.c. of alcohol, and kept, when a pasty, crystalline mass separated. This was collected, washed with alcohol, drained on porous porcelain, and dried at 100°. It amounted to 2·3 grams, and melted and decomposed at 210° after sintering from 180°. On crystallisation from 20 c.c. of boiling water it gave 1·4 grams of the crude hydrogen oxalate of base C, which melted and decomposed at 231°. The conversion of this into pure base C is described on p. 440.

The alcoholic mother liquors of the hydrogen oxalates were distilled to remove alcohol, dissolved in water, and the bases regenerated into ether by means of aqueous sodium hydroxide. The ethereal residue was dissolved in about 25 c.c. of water containing 4·5 c.c. of 34 per cent. hydrobromic acid, and kept, when a quan-

tity of crude emetine hydrobromide separated. After one crystallisation of the crude product from 10 c.c. of water, 2·5 grams of partly purified emetine hydrobromide were obtained. After several crystallisations from water this salt gave pure emetine hydrobromide, which was identified by its appearance, melting point, specific rotatory power, and analysis; also by the preparation from it of benzoylemetine and *N*-methylemetine hydrobromide.

The first mother liquor of the emetine hydrobromide was mixed with aqueous sodium hydroxide and extracted with ether, when 2·6 grams of syrupy base (containing a little ether) were obtained. This material was redissolved in ether, mixed with 5 grams of benzoic anhydride, and heated for three-quarters of an hour on the water-bath, allowing the ether to escape. The residue was then redissolved in ether, and extracted with very dilute hydrochloric acid. The acid extract was washed twice with ether, then mixed with ammonia, and extracted with ether. The ethereal solution, when dried with anhydrous potassium carbonate, and distilled to a volume of about 50 c.c., began to deposit crude benzoyl*iso*emetine, and, after keeping the solution overnight, 0·8 gram melting at 200° was collected.

*Benzoyliso**emetine*, $C_{36}H_{44}O_5N_2$.

After recrystallisation from acetone, this substance formed bundles of slender prisms which melted sharply at 207—208° (corr.). It is insoluble in water, very sparingly soluble in ether, sparingly so in cold alcohol, acetone, or ethyl acetate, but readily so in chloroform. It suffers no loss at 110°. Found, C = 74·1, 73·9; H = 7·6, 7·7; N = 5·0; OMe = 21·0.

$C_{36}H_{44}O_5N_2$ (584·6) requires C = 73·9; H = 7·6; N = 4·8; 4OMe = 21·2 per cent.

0·3273 Gram dissolved in alcohol required 5·5 c.c. *N*/10-H_2SO_4, using cochineal; whence equivalent = 595. The substance is therefore monobasic. Direct proof of the presence of the benzoyl group in this compound was obtained by the hydrolysis of 0·5 gram of the substance with 10 c.c. of concentrated hydrochloric acid for three hours at 150°, and extraction of the liquid with ether, when 0·09 gram of benzoic acid were obtained. Under the same conditions, 0·5 gram of benzoylemetine (T., 1914, **105**, 1614) gave 0·1 gram of benzoic acid.

The specific rotatory power of benzoyl*iso*emetine was determined in chloroform solution:

α_D +2·07°; c = 2·115; l = 2-dcm.; $[\alpha]_D$ +48·9°.

For comparison, the specific rotatory power of benzoylemetine was determined under the same conditions:

$$\alpha_D -2{\cdot}95;\ c=2{\cdot}367;\ l=2\text{-dcm.};\ [\alpha]_D -62{\cdot}3.$$

Base C, $C_{28}H_{38}O_3N_2$ (*or* $C_{29}H_{38}O_3N_2$).

The hydrogen oxalate described on p. 438 is not a pure substance. When the base is regenerated from it, dissolved in ether, and the ethereal solution concentrated, base C crystallises out, and after removing the crystals the ethereal mother liquor yields a syrup on concentration.

Base *C* is readily purified by recrystallisation from ethyl acetate, from which it separates in large, clear, colourless plates which are bevelled at opposite ends. It softens at 126° and melts at 128° (corr.). It is insoluble in water or aqueous sodium hydroxide, but readily soluble in dilute acids. It is easily soluble in alcohol, ethyl acetate, acetone, benzene, or chloroform, fairly easily soluble in ether, sparingly so in hot, and very sparingly so in cold, light petroleum.

It suffers no loss when dried under diminished pressure:

Found: C = 74·8, 74·9, 75·1; H = 8·5, 8·4, 8·4; OMe = 20·2.

$C_{28}H_{38}O_3N_2$ (450·5) requires C = 74·6; H = 8·5; 3OMe = 20·7 per cent.

$C_{29}H_{38}O_3N_2$ (462·5) requires C = 75·3; H = 8·3; 3OMe = 20·1 per cent.

When titrated in aqueous alcoholic solution with cochineal, 0·1964 required 8·65 c.c. *N*/10-sulphuric acid, whence equivalent weight = 227.

The specific rotatory power was determined in chloroform solution:

$$\alpha_D -5{\cdot}18°;\ c=3{\cdot}914;\ l=2\text{-dcm.};\ [\alpha]_D -66{\cdot}2°.$$

The *sulphate* crystallises from water in glistening, prismatic needles which melt and decompose at 289° (corr.). It is sparingly soluble in cold, more readily so in boiling water, and very sparingly so in alcohol.

Found: air-dried salt lost at 100° under reduced pressure, 2·7; at 120° under reduced pressure, 3·6.

$C_{28}H_{38}O_3N_2,H_2SO_4,H_2O$ requires $H_2O = 3{\cdot}2$ per cent.

Found, in the salt dried at 120° under reduced pressure: C = 61·4; H = 7·6.

$C_{28}H_{38}O_3N_2,H_2SO_4$ (548·5) requires C = 61·3; H = 7·4 per cent.

$C_{29}H_{38}O_3N_2,H_2SO_4$ (560·5) „ C = 62·1; H = 7·2 „ „

The specific rotatory power was determined in aqueous solution:

$$\alpha_D +0{\cdot}63°;\ c=2{\cdot}101;\ l=2\text{-dcm.};\ [\alpha]_D +15{\cdot}0°,$$

and on diluting 14·4 c.c. of this solution to 28·2 c.c.:

$$\alpha_D +0{\cdot}38°;\ c=1{\cdot}073;\ l=2\text{-dcm.};\ [\alpha]_D +17{\cdot}7°.$$

The *hydrogen oxalate* crystallises from water in short, glistening needles, usually aggregated to form wart-like masses. It melts and decomposes at 242° (corr.). It is sparingly soluble in cold water, but more readily so in hot water. The air-dried salt loses 1—2 per cent. in a vacuum.

Found, in the salt dried in a vacuum: C = 61·5, 61·5; H = 6·9, 6·7.

$C_{28}H_{38}O_3N_2,2C_2H_2O_4$ (630·5) requires C = 60·9; H = 6·7 per cent.
$C_{29}H_{38}O_3N_2,2C_2H_2O_4$ (642·5) „ C = 61·7; H = 6·6 „ „

The specific rotatory power was determined in aqueous solution:

$$\alpha_D +0{\cdot}58°;\ c=2{\cdot}039;\ l=2\text{-dcm.};\ [\alpha]_D +14{\cdot}2°.$$

Benzoyl Derivative of Base C.

Three grams of base *C* and 5 grams of benzoic anhydride were heated together for two hours on the water-bath. The residue was dissolved in ether, and shaken with dilute hydrochloric acid, when a viscous solid was deposited on the sides of the separator. After separating the ethereal solution of benzoic acid and benzoic anhydride, the deposit and aqueous liquor were washed with ether, and then extracted with chloroform, which dissolved the deposit completely. The chloroform extract was shaken with aqueous sodium carbonate, dried with anhydrous potassium carbonate, and distilled to remove the solvent. The residue was mixed with ether, when it crystallised as a colourless, chalky mass, which amounted to 3·2 grams and melted at 177° (corr.). The specific rotatory power was determined in chloroform solution:

$$\alpha_D +3{\cdot}88°;\ c=4{\cdot}314;\ l=2\text{-dcm.};\ [\alpha]_D +45{\cdot}0°.$$

On crystallisation from acetone, the substance was obtained in fine needles of the same specific rotatory power (Found, in chloroform: $c=4{\cdot}213$; $[\alpha]_D +44{\cdot}5°$), but apparently in a dimorphous form, for when placed in a bath at 150° it melted and resolidified and then melted again about 176° (corr.), whilst when placed in a bath at 100° it sintered at about 120°, but did not melt until 175—176° (corr.). It suffered no loss in a vacuum.

Found: C = 76·1, 76·4; H = 7·4, 7·8.

$C_{35}H_{42}O_4N_2$ (554·5) requires C = 75·8; H = 7·6 per cent.
$C_{36}H_{42}O_4N_2$ (566·5) „ C = 76·3; H = 7·5 „ „

The base was titrated in aqueous-alcoholic solution with hydrochloric acid, using cochineal as an indicator. The end-point was not

sharp, but the result indicates clearly that the substance is monobasic:

0·9176 required 15·9 c.c. $N/10$-acid; whence equivalent = 577.

The base, crystallised from acetone, is insoluble in boiling water, fairly soluble in cold, but easily so in hot alcohol, ethyl acetate, or acetone, and easily soluble in chloroform. With ether it shows a curious behaviour, becoming gradually transformed into a bulky, cotton-wool-like mass of fine needles, which represent the original form of the substance and melt sharply at 177° (corr.). An analysis of the substance in this crystalline form gave a similar result to that obtained with the crystals from acetone. (Found: C = 76·4; H = 7·7.)

The base is insoluble in water or in aqueous sodium hydroxide, but dissolves in very dilute solutions of mineral acids, forming sparingly soluble salts.

The *sulphate* separated on the spontaneous evaporation of an aqueous-alcoholic solution as a jelly, which gradually changed to a mass of colourless, felted needles.

The Properties of Emetamine and its Salts.

Emetamine crystallises from ethyl acetate in colourless needles which melt at 155—156° (corr.). It is insoluble in hot water or in aqueous alkalis, but dissolves readily in dilute acids, giving colourless solutions. Neither the base nor its salts give fluorescent solutions. Emetamine is easily soluble in alcohol, ethyl acetate, acetone, benzene, or chloroform, sparingly so in ether, and almost insoluble in light petroleum. It dissolves in concentrated sulphuric acid, giving a very pale yellow solution having a green tinge, and this solution becomes yellowish-brown on the addition of a drop of nitric acid. It dissolves in an excess of Froehde's reagent, giving an emerald-green solution. Solutions of emetamine in dilute hydrochloric acid give granular, amorphous precipitates with picric acid, gold chloride, or platinic chloride.

Emetamine suffers no loss when heated in a vacuum at 100°:
Found, C = 73·2, 73·4; H = 7·5, 7·5.

$C_{29}H_{36}O_4N_2$ (476·5) requires C = 73·1; H = 7·6 per cent.
$C_{30}H_{36}O_4N_2$ (488·5) requires C = 73·7; H = 7·4 per cent.

On titration with methyl-orange as indicator, 0·6460 required 27·0 c.c. $N/10$-HCl, whence equivalent = 239.

Emetamine is dextrorotatory, determinations of the specific rotatory power giving the following results:

In chloroform: α_D +1·37°; $c = 6·140$; $l = 2$-dcm.; $[\alpha]_D$ +11·2°.
α_D +0·85°; $c = 4·275$; $l = 2$-dcm.; $[\alpha]_D$ +9·9°.

In commercial absolute alcohol: $[\alpha]_D$ +0·52°; c=2·113; l=2-dcm.; $[\alpha]_D$ +12·3°.

Emetamine hydrobromide crystallises from water in colourless, glistening, prismatic needles which contain $7H_2O$. After drying in a vacuum over sulphuric acid, it sinters from 210° and gradually melts, without flowing, up to about 225° (corr.). It is sparingly soluble in cold, easily so in hot water. It is precipitated from its aqueous solution on the addition of sodium bromide.

Found, loss in a vacuum at 120°, 16·4.

$C_{29}H_{36}O_4N_2,2HBr,7H_2O$ requires H_2O=16·5 per cent.

Found, in the dried salt: C=54·8, 54·9; H=6·4, 6·4; Br=24·7; OMe=20·0; NMe=0.

$C_{29}H_{36}O_4N_2,2HBr$ (638·3) requires C=54·6; H=6·0; Br=25·0; 4OMe=19·4 per cent.

$C_{30}H_{36}O_4N_2,2HBr$ (650·3) requires C=55·4; H=5·9; Br=24·6; 4OMe=19·1 per cent.

The specific rotatory power of the hydrated salt was determined in aqueous solution:

α_D −3·90°; c=8·042; l=2-dcm.; $[\alpha]_D$ −24·3°.

α_D −1·83°; c=4·156; l=2-dcm.; $[\alpha]_D$ −22·0°.

Emetamine hydrogen oxalate separates in colourless rosettes of small needles containing $3H_2O$ on the addition of an alcoholic solution of hydrated oxalic acid tc an alcoholic solution of the base. After drying in a vacuum over sulphuric acid, it sinters from about 165° and effervesces at 171° (corr.).

This salt is easily soluble in water, but almost insoluble in alcohol.

Found, loss in a vacuum at 110°, 7·6, 7·9.

$C_{29}H_{36}O_4N_2,2C_2H_2O_4,3H_2O$ requires H_2O=7·6 per cent.

Found, in the dried salt: C=60·8, 60·8; H=6·4, 6·3.

$C_{29}H_{36}O_4N_2,2C_2H_2O_4$ (656·5) requires C=60·3; H=6·1 per cent.

$C_{30}H_{36}O_4N_2,2C_2H_2O_4$ (668·5) requires C=61·1; H=6·0 per cent.

The specific rotatory power of the hydrated salt was determined in aqueous solution:

α_D −0·47°; c=3·920; l=2-dcm.; $[\alpha]_D$ −6·0°.

Emetamine can be recovered unchanged after being heated with one and a-half times its weight of benzoic anhydride for one hour on the water-bath.

It undergoes reduction when treated with sodium and alcohol under the conditions employed for the reduction of methylpsychotrine. 2·8 Grams of emetamine were reduced by 3·0 grams of sodium and sufficient absolute alcohol, the product being separated into non-phenolic and phenolic bases in the usual way.

The non-phenolic base did not crystallise and did not yield a crystalline hydrogen oxalate in alcoholic solution. An attempt to crystallise the hydrobromide from aqueous solution being also unsuccessful, the base was benzoylated under the conditions employed for the benzoylation of methylpsychotrine, when the ethereal solution of the benzoylated base deposited 0·3 gram of pale yellow crystals melting at 185—187°. After one crystallisation from acetone, this substance melted at 204° (corr.), and, after a second, formed colourless, prismatic needles which melted at 205° (corr.), whilst benzoyl*iso*emetine melted at 206° in the same bath, and a mixture of the two compounds at 204°.

The Properties of N-*Methylemetine and its Salts.*

N-Methylemetine hydrobromide and hydriodide were described in the earlier paper (T., 1914, **105**, 1618). A considerable quantity of the former being available, the opportunity was taken of subjecting it to a prolonged fractional crystallisation. The crude salt (133 grams) was crystallised many times and the products collected in three crops of 101, 10·5, and 9·0 grams. Each had the melting point previously recorded, and no significant difference was shown between the specific rotatory powers of the first and last crop in aqueous solution; the figures were $[\alpha]_D$ +5·6° (c=5·141) and $[\alpha]_D$ +5·7° (c=4·972) respectively.

The free base has not been obtained in a crystalline form, but its specific rotatory power has been determined in the following manner. The base was regenerated from a solution of the pure hydrobromide by means of sodium carbonate and extracted with chloroform. The chloroform solution was dried with anhydrous sodium sulphate and filtered. Five c.c. were then evaporated to dryness and titrated with *N*/10-sulphuric acid, using cochineal, whence the concentration of the solution (c) could be calculated. The following results were thus obtained for a chloroform solution of the base in two separate experiments:

α_D −4·03°; c=3·83; l=2-dcm.; $[\alpha]_D$ −52·6°
α_D −5·0°; c=4·70; l=2-dcm.; $[\alpha]_D$ −53·2°.

Methylemetine sulphate has now been obtained in a crystalline form. For its preparation, methylemetine regenerated from the pure hydrobromide was dissolved in three to four times its weight of absolute alcohol and neutralised by the addition of 50 per cent. aqueous sulphuric acid. On keeping, the salt separated in colourless, prismatic needles which, after drying at 100°, softened from 210° and melted at 217° (corr.):

Found, in the air-dried salt: loss at 120° = 6·4; C = 56·3, 56·5; H = 7·8, 7·8; SO_4 = 15·0.

$C_{30}H_{42}O_4N_2,H_2SO_4,2\frac{1}{2}H_2O$ (637·6) requires H_2O = 7·1; C = 56·5; H = 7·7; SO_4 = 15·1 per cent.

On another occasion the salt was found to contain rather more water of crystallisation.

Found, in the air-dried salt: loss at 120° = 8·1.

$C_{30}H_{42}O_4N_2,H_2SO_4,3H_2O$ (646·6) requires H_2O = 8·4 per cent.

Found, in the salt dried at 120°: C = 61·0; H = 7·6.

$C_{30}H_{42}O_4N_2,H_2SO_4$ (592·6) requires C = 60·8; H = 7·5 per cent.

Methylemetine sulphate is very easily soluble in water, 1 gram dissolving in about 2·3 c.c. of cold water; it is very sparingly soluble in absolute alcohol.

The specific rotatory power of the salt containing $3H_2O$ was determined in aqueous solution:

$$\alpha_D + 0{\cdot}67°;\ c = 4{\cdot}372;\ l = 2\text{-dcm.};\ [\alpha]_D + 7{\cdot}7°.$$

Methylemetinemethine, $C_{32}H_{46}O_4N_2$.

Twenty-five grams of methylemetine methiodide (containing $3H_2O$) were dissolved in 500 c.c. of boiling water and digested with the silver hydroxide prepared from 12 grams of silver nitrate until the solution no longer contained dissolved iodide. The solution was then filtered, and evaporated to dryness under the diminished pressure afforded by a good water-pump. After the residue was dry, the heating was continued for a further period of one and a-half hours, also in a partial vacuum. The crude methine was then dissolved in dilute hydrochloric acid, regenerated by means of sodium carbonate, and extracted with ether. The residue after distillation of the ether formed a nearly colourless gum, which was neutralised with a 20 per cent. aqueous solution of oxalic acid, and kept, when 11·7 grams of the pure methine oxalate separated in large crystals. On concentrating the mother liquors two further crops of 3·9 and 1·8 grams were obtained in an almost equally pure state, so that the total yield is 17·4 grams, that is, 77 per cent. of that theoretically obtainable.

Methylemetinemethine oxalate crystallises from water in large, hard, brilliant prisms, which contain $7\frac{1}{2}H_2O$ and melt at 82—83° (corr.). It is very easily soluble in water, alcohol, or acetone.

Found: loss in a vacuum over H_2SO_4 = 18·1; 17·9.

$C_{32}H_{46}O_4N_2,C_2H_2O_4,7\frac{1}{2}H_2O$ (747·7) requires H_2O = 18·1 per cent.

Found, in the salt dried in a vacuum: C=66·4, 66·6; H=8·0, 8·1; N=4·7.

$C_{32}H_{46}O_4N_2,C_2H_2O_4$ (612·6) requires C=66·6; H=7·9; N=4·6 per cent.

The specific rotatory power of the hydrated salt was determined in aqueous solution:

α_D −1·98°; c=4·879; l=2-dcm.; $[\alpha]_D$ −20·3°.
α_D −1·13°; c=2·439; l=2-dcm.; $[\alpha]_D$ −23·2°.
α_D −0·60°; c=1·220; l=2-dcm.; $[\alpha]_D$ −24·6°.

The *base* is precipitated as a white, granular powder on the addition of sodium carbonate to an aqueous solution of the oxalate. When viewed under the microscope it does not appear to be crystalline, and it has no sharp melting point, but gradually sinters and melts without flowing between 45° and 55°. It can readily be filtered, and washed with cold water. After drying in the air it retains 1·5 per cent. of moisture, which is lost in a vacuum.

Found, for vacuum-dried base: C=73·1, 73·0; H=9·0, 9·0.

$C_{32}H_{46}O_4N_2$ (522·5) requires C=73·5; H=8·9 per cent.

When the base is kept for several months it changes from a white, granular powder to a pale straw-coloured, glassy mass, which can be ground to a white powder having the original melting point; this behaviour confirms the view that the substance is amorphous.

It is practically insoluble in water, but easily soluble in the usual organic solvents, including light petroleum. It dissolves in concentrated sulphuric acid, giving a golden-brown solution, which becomes deep chestnut-brown on the addition of a drop of nitric acid. It dissolves in Froehde's reagent, giving a solution which is momentarily brown, but gradually changes through a neutral tint to a dirty indigo.

The *platinichloride* is precipitated as an amorphous, yellowish-brown powder on the addition of platinic chloride to a solution of the base in dilute hydrochloric acid. The air-dried salt lost 7·4 per per cent. at 110°, and the dried salt gave Pt=20·84. $C_{32}H_{46}O_4N_2,H_2PtCl_6$ (932·5) requires Pt=20·93 per cent.

The hydrobromide, hydriodide, and methiodide did not crystallise.

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